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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,025	REILLY, JENNIFER OTT	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,10,11 and 13-28* is/are pending in the application.

4a) Of the above claim(s) *5,10 and 13-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,6 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 2/2/04, have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Maintained Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6, 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

As set forth previously, the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a "hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

Applicant does not appear to address this aspect of the prior rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting the survival of cholinergic neurons, comprising the administration of a mammalian sonic hedgehog polypeptide (e.g. SEQ ID NO: 15) or the N-terminal autoproteolytic fragment thereof, does not reasonably provide enablement for such methods comprising the administration of polypeptides other than a naturally occurring mammalian sonic hedgehog polypeptide or for the genus of "bioactive fragments" thereof. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims, as set forth previously and reiterated below.

The specification presents the results obtained with an *in vitro* model of cholinergic cell survival comprising the administration of sonic hedgehog, presumably that of the murine SEQ ID NO: 12, although it does not appear that the specification actually teaches which sonic hedgehog is used. The claims claim methods using any polypeptide that could be termed a "hedgehog" polypeptide, yet the specification has not provided sufficient guidance as to which other polypeptides would work as claimed. One of skill in the art appreciates that the many known hedgehog polypeptides provide for a tremendous and disparate array of developmental controls, determining cell fates in embryonic muscle, lung, and nervous tissues. There is no

teaching in the specification as to which of this vast array of proteins, natural or created, could be used in the claimed methods. The prior art is also silent as to which of the proteins, with the exception of sonic hedgehog (see below) could be used to practice the claimed methods. One could only guess at which, if any, could be used; and one of skill in the art would certainly not expect that all could be used. In fact, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that in the art of treatment of neuronal cells with hedgehog proteins, the specificity of the hedgehog polypeptide is critical in some unknown way, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Additionally, Claims 2 requires the use of a "bioactive fragment" of a hedgehog protein, yet the specification has simply presented an invitation to the skilled artisan to try to find such fragments other than that corresponding to the naturally occurring N-terminal autoproteolytic fragment (e.g. claim 4). The art recognizes that it is this fragment that is required for activity and that even small deletions of it abolish activity, see Marti, S. et al., Nature 375(322-325)1995, particularly col 1 of page 323 and Figure 1a. Further, the claims encompass variants of the disclosed sonic hedgehog polypeptides, i.e., the specification contemplates such variants as being encompassed by the term "hedgehog polypeptide" (see pages 31-36 for example), yet the specification has not provided sufficient guidance as to how to make such variants. One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a hedgehog polypeptide, and through trial and error experimentation is left

to determine when a polypeptide is obtained that could used to improve the survival of cholinergic neurons. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-

dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues, essentially, that because the claims are now structured in a means plus function format that they must be enabled and be supported by an adequate written description. This argument has been fully considered but not deemed persuasive.

One skilled in the art appreciates that simply writing down or verbalizing that a "means" have a particular function in no way enables one to make such a means and nor does it put one in possession of a means. Applicant's additional questioning of the basis of the rejection has been thoroughly discussed in the original rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, and 11 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5884079 to Ingham et al., in view of Molses et al., Journal of Neuroscience 15(12)8131-8142)1995.

The specification discloses that administration of hedgehog proteins along with certain neurotrophic factors can promote the survival of a variety of neuron cell types, each of which are known in the art to be lost in particular neurodegenerative diseases, e.g. Parkinson, Huntington, and Alzheimer's diseases. A specific embodiment of the instant claims is a method of promoting the survival of cholinergic neurons of the basal forebrain, either *in vivo* or *in vitro*, comprising the co administration of the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. residues 24-197 of SEQ ID NO: 15) and nerve growth factor (NGF) e.g. pages71-75. The specification indicates that such neurons are known to degenerate in Alzheimer's disease, e.g. pages 62-63, and that these neurons are also useful for *in vitro* studies regarding the effects of neurotrophic factors on them (particularly the effect of sonic hedgehog), as is well established in the art. e.g. see page 71.

U.S. Patent No: 5884079 also discloses that the above disorders and associated neurons can be treated with the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. col 46) and that such treatment can be in combination with the administration of an appropriate neurotrophic factor, e.g. CNTF, BDNF or NGF, see col 47, Lines 27- 38. More particularly U.S. Patent No: 5884079 discloses that cholinergic neurons of the basal forebrain (those of the nucleous basalis), that degenerate in Alzheimer's disease, can be treated with sonic hedgehog proteins (col 46, L38-47). U.S. Patent No: 5884079 does not, however, specifically state which additional

neurotrophic factors would be appropriate to use in the context of Alzheimer's disease. Specifically, U.S. Patent No: 5884079 does not disclose that NGF is trophic for the cholinergic neurons of the basal forebrain as is required by the embodiment of the instant claims referred to above. However, an artisan of ordinary skill appreciates that the survival-promoting effects of NGF on cholinergic neurons of the basal forebrain is well established and old in the art, see Molses et al. who teach that treatment of rats *in vivo* with NGF promotes the survival of basal forebrain cholinergic neurons (see the Abstract).

Therefore, it would be obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, to promote the survival of cholinergic neurons of the basal forebrain (nucleous basalis) by administering a trophic amount of the autoproteolytic fragment of sonic hedgehog and another appropriate neurotrophic factor including CNTF, BDNF and NGF, as taught and suggested by Patent No: 5884079 (cols 46-47) and to use NGF as the particular neurotrophic factor as taught by Molses et al. The motivation to do so is provided by Patent No: 5884079 wherein it is taught that neuronal degenerative disorders such as Alzheimer's disease can be treated with sonic hedgehog in combination with appropriate neurotrophic factors (cols 46-47) and Molses et al. who teach that NGF is an appropriate factor to use on the particular neurons involved in Alzheimer's disease, e.g. the cholinergic neurons of the basal forebrain, see the Abstract.

Applicant argues that prior art does not teach or suggest the synergistic activity of hedgehog and a neurotrophic factor. This argument has been fully considered but not deemed persuasive. That these factors behave synergistically is an inherent property of them being used together as taught by U.S. Patent No: 5884079.

Conclusion

This application contains claims 5, 10, 13-28 are drawn to an invention nonelected with traverse in Paper No 17. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

April 22, 2004

LORRAINE SPECTOR
PRIMARY EXAMINER